09/980194 JC14 Rec'd PCT/PTO 15 NOV 2001

Practitioner's Docket No. 81785

CHAPTER II

Preliminary Classification:
Proposed Class:
Subclass:

NOTE: "All applicants are requested to include a preliminary classification on newly filed patent applications. The preliminary classification, preferably class and subclass designations, should be identified in the upper right-hand corner of the letter of transmittal accompanying the application papers, for example 'Proposed Class 2, subclass 129.'" M.P.E.P., § 601, 7th ed.

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US)

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

PCT/DE00/01540	12 MAY 2000	14 MAY 1999
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED

VORRICHTUNG UND VERFAHREN ZUR PHOTOLITHOGRAPHISCHEN BELICHTUNG VON BIOLOGISCHEN STOFFEN
TITLE OF INVENTION

ARON BRAUN AND ARNO HEUERMANN
APPLICANT(S)

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

CERTIFICATION UNDER 37 C.F.R. § 1.10*
(Express Mail label number is mandatory.)
(Express Mail certification is optional.)

I hereby certify that this Transmittal Letter and the papers indicated as being transmitted therewith is being deposited with the United States Postal Service on this date November 14, 2001, in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL919995207US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

EDWARD M. KRIEGSMAN
(type or print name of person mailing paper)

Edward M. Kriegsman
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

***WARNING:** Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

NOTE: To avoid abandonment of the application, the applicant shall furnish to the USPTO, not later than 20 months from the priority date: (1) a copy of the international application, unless it has been previously communicated by the International Bureau or unless it was originally filed in the USPTO; and (2) the basic national fee (see 37 C.F.R. § 1.492(a)). The 30-month time limit may not be extended. 37 C.F.R. § 1.495.

***WARNING:** Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. § 1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing—See 37 C.F.R. § 1.8.*

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 U.S.C. § 371 otherwise the submission will be considered as being made under 35 U.S.C. § 111. 37 C.F.R. § 1.494(f).

I. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. § 371:

a. ☒ This express request to immediately begin national examination procedures (35 U.S.C. § 371(f)).

b. ☒ The U.S. National Fee (35 U.S.C. § 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2. Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
☐*	TOTAL CLAIMS	19 −20=	0	× $18.00=	$ 0
	INDEPENDENT CLAIMS	2 −3=	0	× $78.00=	0
	MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ ~~$260.00~~ 280	280
BASIC FEE**	☐ U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: ☐ and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(1) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 C.F.R. § 1.492(a)(4)) ..... $96.00 ☐ and the above requirements are not met (37 C.F.R. § 1.492(a)(1)) ..... $670.00 ☒ U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: ☐ has been paid (37 C.F.R. § 1.492(a)(2)) ..... $690.00 ☐ has not been paid (37 C.F.R. § 1.492(a)(3)) ..... $970.00 ☒ where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 C.F.R. § 1.492(a)(5)) ..... ~~$840.00~~ 890				890
	Total of above Calculations				= 1170
SMALL ENTITY	Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed also. (note 37 C.F.R. § 1.9, 1.27, 1.28)				− 585
	Subtotal				585
	Total National Fee				$ 585
	Fee for recording the enclosed assignment document $40.00 (37 C.F.R. § 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				0
TOTAL	Total Fees enclosed				$ 585

APPLICANT IS A SMALL ENTITY

*See attached Preliminary Amendment Reducing the Number of Claims.

i. ☒ A check in the amount of 585 to cover the above fees is enclosed.

ii. ☐ Please charge Account No. _____ in the amount of $ _____. A duplicate copy of this sheet is enclosed.

***WARNING:** *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. ☒ A copy of the International application as filed (35 U.S.C. § 371(c)(2)):

NOTE: Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment. "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.

a. ☒ is transmitted herewith.

b. ☐ is not required, as the application was filed with the United States Receiving Office.

c. ☐ has been transmitted

i. ☐ by the International Bureau.
Date of mailing of the application (from form PCT/1B/308): _____.

ii. ☐ by applicant on _____.
Date

4. ☒ A translation of the International application into the English language (35 U.S.C. § 371(c)(2)):

a. ☐ is transmitted herewith.

b. ☐ is not required as the application was filed in English.

c. ☐ was previously transmitted by applicant on _____.
Date

d. ☒ will follow.

5. ☒ Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. § 371(c)(3)):

NOTE: The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.

a. ☐ are transmitted herewith.

b. ☐ have been transmitted

i. ☐ by the International Bureau.
Date of mailing of the amendment (from form PCT/1B/308): _____.

ii. ☐ by applicant on (date) _____.
Date

c. ☒ have not been transmitted as

i. ☒ applicant chose not to make amendments under PCT Article 19.
Date of mailing of Search Report (from form PCT/ISA/210.): October 9, 2000

ii. ☐ the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. ☒ A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. § 371(c)(3)):

a. ☐ is transmitted herewith.

b. ☐ is not required as the amendments were made in the English language.

c. ☒ has not been transmitted for reasons indicated at point 5(c) above.

7. ☒ A copy of the international examination report (PCT/IPEA/409)

☒ is transmitted herewith.

☐ is not required as the application was filed with the United States Receiving Office.

8. ☐ Annex(es) to the international preliminary examination report

a. ☐ is/are transmitted herewith.

b. ☐ is/are not required as the application was filed with the United States Receiving Office.

9. ☐ A translation of the annexes to the international preliminary examination report

a. ☐ is transmitted herewith.

b. ☐ is not required as the annexes are in the English language.

10. ☒ An oath or declaration of the inventor (35 U.S.C. § 371(c)(4)) complying with 35 U.S.C. § 115

a. ☐ was previously submitted by applicant on _____. Date

b. ☐ is submitted herewith, and such oath or declaration

i. ☐ is attached to the application.

ii. ☐ identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. § 1.70.

c. ☒ will follow.

II. Other document(s) or information included:

11. ☒ An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):

a. ☒ is transmitted herewith.

b. ☐ has been transmitted by the International Bureau. Date of mailing (from form PCT/IB/308): _____.

c. ☐ is not required, as the application was searched by the United States International Searching Authority.

d. ☐ will be transmitted promptly upon request.

e. ☐ has been submitted by applicant on _____. Date

12. ☐ An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98:

a. ☐ is transmitted herewith.

Also transmitted herewith is/are:

☐ Form PTO-1449 (PTO/SB/08A and 08B).

☐ Copies of citations listed.

b. ☐ will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. § 371(c).

c. ☐ was previously submitted by applicant on _____. Date

13. ☐ An assignment document is transmitted herewith for recording.

A separate ☐ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or ☐ FORM PTO 1595 is also attached.

_____

_____

_____

14. ☐ Additional documents:

a. ☐ Copy of request (PCT/RO/101)

b. ☐ International Publication No. _____

i. ☐ Specification, claims and drawing

ii. ☐ Front page only

c. ☐ Preliminary amendment (37 C.F.R. § 1.121)

d. ☐ Other

_____

_____

_____

15. ☒ The above checked items are being transmitted

a. ☒ before 30 months from any claimed priority date.

b. ☐ after 30 months.

16. ☐ Certain requirements under 35 U.S.C. § 371 were previously submitted by the applicant on _____, namely:

_____

_____

_____

_____

_____

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependant claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

☒ The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 11-1755.

☐ 37 C.F.R. § 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

☐ 37 C.F.R. § 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

☐ 37 C.F.R. § 1.17 (application processing fees)

☐ 37 C.F.R. § 1.17(a)(1)–(5) (extension fees pursuant to § 1.136(a).

☐ 37 C.F.R. § 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. § 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).

NOTE: 37 C.F.R. § 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

☐ 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

SIGNATURE OF PRACTITIONER

Reg. No.: 33,529

Tel. No.: (508) 879-3500

Customer No.: 23685

EDWARD M. KRIEGSMAN
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09/980194

Rec'd PCT/PTO 23 JUL 2002

PATENT
Attorney Docket No. 81785

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
ARON BRAUN ET AL.	)	
	)	
Serial No.: 09/980,194	)	Group Art Unit: Unknown
	)	
Int'l. Appln. Filed: May 12, 2000	)	Examiner: Unknown
	)	
For: DEVICE AND METHOD FOR PHOTOLITHOGRAPHICALLY IRRADIATING BIOLOGICAL SUBSTANCES	)	

Box PCT
Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Prior to examination of the above-identified patent application, please enter the amendment below.

IN THE CLAIMS:

Please amend claims 4-8, 11-13 and 19 as follows:

4. (Amended) The device according to claim 1, further characterized in that luminous diodes and/or optical switches are arranged for the control of the individual optical fibers.

5. (Amended) The device according to claim 1, further characterized in that the substances to be exposed are introduced directly at the ends of the optical fibers.

6. (Amended) The device according to claim 1, further characterized in that the substances to be exposed are arranged on a separate support.

7. (Amended) The device according to claim 1, further characterized in that the substances to be exposed are arranged on a separate support, whereby this support is a DNA chip, a PNA chip or a peptide chip.

8. (Amended) The device according to claim 1, further characterized in that the device additionally comprises at least one detector.

11. (Amended) The device according to claim 1, further characterized in that a dynamic mask is provided for the control of the individual optical fibers.

12. (Amended) The device according to claim 1, further characterized in that a set of static masks is provided for the control of the individual optical fibers.

13. (Amended) The device according to claim 1, further characterized in that the light source emits a spectrum of wavelengths that bring about the deprotecting of nucleotides, nucleotide analogs and peptide nucleic acid building blocks for the elongation of the chain and for the construction of oligomers, and that between this light source and the substrate is arranged a bundle of optical fibers, to which light can be selectively coupled each time by targeted control, and that the solid phase on which the oligomer synthesis occurs is positioned precisely and rigidly behind the bundle of optical fibers, and that the solid phase on which oligomer synthesis occurs is arranged in a chamber in which the solutions and/or reagents necessary for the DNA or PNA synthesis can be introduced onto this solid phase by other devices.

19. (Amended) The method according to claim 16, further characterized in that a device for the photolithographic exposure of biological substances is used for conducting the method, said

device comprising at least one light source, a bundle of light-guide optical fibers, and a control unit, wherein each of the optical fibers can be controlled by light and/or light can be coupled to these fibers, independently of one another.

REMARKS

No claims have been canceled herein. Claims 4-8, 11-13 and 19 have been amended herein. No new claims have been added herein. Therefore, claims 1-19 are under active consideration.

It is respectfully submitted that the present application is in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is

required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Kriegsman & Kriegsman

By: _____

Edward M. Kriegsman
Reg. No. 33,529
665 Franklin Street
Framingham, MA 01702
(508) 879-3500

Dated: July 17, 2002

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Box PCT, Commissioner for Patents, Washington, D.C. 20231 on July 17, 2002

_____
Edward M. Kriegsman
Reg. No. 33,529
Dated: July 17, 2002

MARKED-UP AMENDED CLAIMS 4-8, 11-13 AND 19

4. (Amended) The device according to [one of the preceding claims] claim 1, further characterized in that luminous diodes and/or optical switches are arranged for the control of the individual optical fibers.

5. (Amended) The device according to [one of the preceding claims] claim 1, further characterized in that the substances to be exposed are introduced directly at the ends of the optical fibers.

6. (Amended) The device according to [one of the preceding claims] claim 1, further characterized in that the substances to be exposed are arranged on a separate support.

7. (Amended) The device according to [one of the preceding claims] claim 1, further characterized in that the substances to be exposed are arranged on a separate support, whereby this support is a DNA chip, a PNA chip or a peptide chip.

8. (Amended) The device according to [one of the preceding claims] claim 1, further characterized in that the device additionally comprises at least one detector.

11. (Amended) The device according to [one of the preceding claims] claim 1, further characterized in that a dynamic mask is provided for the control of the individual optical fibers.

12. (Amended) The device according to [one of the preceding claims] claim 1, further characterized in that a set of static masks is provided for the control of the individual optical fibers.

13. (Amended) The device according to [one of the preceding claims] claim 1, further characterized in that the light source emits a spectrum of wavelengths that bring about the deprotecting of nucleotides, nucleotide analogs and peptide nucleic acid building blocks for the elongation of the chain and for the construction of oligomers, and that between this light source and

the substrate is arranged a bundle of optical fibers, to which light can be selectively coupled each time by targeted control, and that the solid phase on which the oligomer synthesis occurs is positioned precisely and rigidly behind the bundle of optical fibers, and that the solid phase on which oligomer synthesis occurs is arranged in a chamber in which the solutions and/or reagents necessary for the DNA or PNA synthesis can be introduced onto this solid phase by other devices.

19. (Amended) The method according to claim 16, further characterized in that a device [according to claim 1] for the photolithographic exposure of biological substances is used for conducting the method, said device comprising at least one light source, a bundle of light-guide optical fibers, and a control unit, wherein each of the optical fibers can be controlled by light and/or light can be coupled to these fibers, independently of one another.

DEVICE AND METHOD FOR PHOTOLITHOGRAPHICALLY IRRADIATING BIOLOGICAL SUBSTANCES

The invention concerns a device and a method for the photolithographic exposure of biological substances.

DNA chips are ultra-small, generally planar surfaces, on which a large number of different oligomers (short, single-stranded DNA molecules) are introduced in a spatially organized manner. Such chips are used, for example, for the parallel recognition of numerous DNA sequences in a prepared tissue specimen. For this purpose, the chip surface is wetted with a solution of single-stranded DNA segments from the tissue specimen. Complementary DNA segments from the solution are deposited on the corresponding oligomers introduced on the chip surface (hybridization). After this, a determination is made of which places on the chip a hybridization has occurred by means of suitable methods, such as, e.g., fluorescent labeling. If one knows where on the chip the respective oligomers are introduced, conclusions can be made relative to the DNA sequences in the tissue specimen. For this purpose, usually a dense rectangular grid is defined on the chip support surface. One type of oligomer is introduced at each grid point in the form of a small spot. The maximum possible number of different DNA sequences on the chip is consequently equal to the number of grid points. Since one wishes to introduce as many types of oligomers as possible on one chip, but the chips must be as small as possible at the same time in order to be able to effectively hybridize, it is an important objective in the production of DNA chips to achieve as high a grid density as possible.

Different methods for DNA chip production are known in the prior art:

1) All oligomers are synthesized individually in a conventional manner in the test tube and then are pipetted onto the provided grid points on the support, typically by an automatic micropipetting device. This method is very time-consuming and expensive, since each oligomer must be prepared or purchased individually and must be introduced by hand into the pipetting device. The grid density is limited by the high angular imprecision of the typical piezoelectric micropipettes that are presently available.

2) The oligomers are synthesized directly on the chip by means of an automatic pipetting device. The oligomer chain provided on each grid point is built up base by base (nucleobases). The chemical method is basically the same as in conventional oligomer synthesis in the test tube. The difference is that all oligomers are produced simultaneously directly at the provided determination site by a single automatic device. The separate operating steps of oligomer synthesis and micropipetting of method 1) are thus combined into one uniform operating step. This in-situ synthesis normally proceeds as follows: The automatic pipetting device sequentially drops the first nucleobase provided for each grid point onto a prepared substrate. This is mechanically not very time-consuming or expensive, since there are only 4 different nucleobases (C, T, G, A). For example, 4 micropipettes coupled to one another can be used for this purpose. After applying the first nucleoside building block at each grid point, the substrate is washed and after a "capping step", the protecting groups at the 5'-OH functions are removed, in order to make possible the reaction with the respective subsequent nucleoside building block. After this, the second

nucleobase is pipetted onto each grid point. The substrate is then washed again and deprotected. In this way, the necessary oligomer chains are constructed step by step on each grid point. This method is not particularly rapid, since each nucleobase must be newly pipetted one after the other onto each grid point. As in the case of method 1), the grid density is limited by the imprecision of the micropipettes. The imprecision is even worse here, since each grid point must be contacted several times sequentially in a way that is as identical as possible.

3) The oligomers are synthesized directly on the support as in 2), but the targeted binding of the correct nucleobases to the correct grid points is done by means of a completely parallel, photolithographic technique instead of sequential, target-precise pipetting steps. The method is based on the fact that the 5'-OH protecting groups of oligonucleotides can be removed in a targeted manner by light of a specific wavelength. By suitable local irradiation patterns, oligonucleotide ends can thus be made capable of reaction at precisely those grid points at which one wishes to introduce a new nucleoside in the next step. By complete wetting of the chip surface with a nucleotide building-block solution, a nucleotide base is thus bound only to the sites that have been previously exposed, and all unexposed sites remain unchanged. The local exposure patterns are produced by positioning a photomicrographic black-white mask between the substrate and the light source. The mask covers all of the grid points, which are not to be made capable of reaction. The elongation of the oligomer chains by one nucleobase at all grid points is then conducted as follows: Those grid points which must be extended by the first of the 4 possible

types of nucleobases (e.g., C) are precisely exposed by means of a first mask. Then the chip is wetted with a solution of the corresponding nucleotide base, whereupon only the exposed points are elongated by this base. Since the newly bound bases all have a protecting group, they do not further react in the following steps until their protecting groups are cleaved by another exposure. The chip is washed after this reaction step. Now, those grid sites, which must be elongated by the second of the 4 possible types of nucleobases (e.g., T) are precisely exposed by means of a second mask. Then the chip is again wetted with a solution of the corresponding nucleotide building block and the exposed sites in this way are elongated by this base. The procedure is the same for the remaining two bases (e.g., G and A). For the elongation of all oligomers by one nucleobase, one consequently requires four exposure steps and 4 photomasks. This method is very efficient due to the high parallel operation, and it is also suitable for obtaining very high grid densities, due to the high precision that can be obtained with photolithography. Of course, the method is very time-consuming and thus expensive, since a large number of photomasks must first be created for the production of a specific type of chip. Also, rigid requirements are placed on the positioning accuracy of the masks during exposure in the case of high grid densities, and these requirements can be fulfilled efficiently only by using very expensive apparatus.

4) The same method is applied as in 3), but instead of the large number of photographic masks, only a single, transmissive, liquid crystal display, which is controlled electronically and serves as a dynamic mask, is used. This method is

simple and inexpensive, since photographic masks need not be produced and there is thus no positioning problem. One possible problem of this method is the limited optical contrast of the liquid crystal displays that are currently available (maximum 1:100). The light intensity ratio between exposed and covered points is thus reduced, which can have as a consequence a reduction in yield in the case of oligomer synthesis.

These methods of the prior art have a number of disadvantages. Of the above-described production methods for DNA chips, the photolithographic method with dynamic liquid crystal masks is the only one that permits a simple, inexpensive and reliable production of chips with high grid density. The deficient contrast of liquid crystal displays, however, has as a consequence a reduction in the quality of the oligomer points, which in the final analysis reduces the detection sensitivity of the chip.

The object of the present invention is thus to create a device, which overcomes the disadvantages of the prior art. Another object of the invention is the creation of another method for the photolithographic exposure of biological substances.

The object is solved by the characterizing features of the main claim. Advantageous embodiments of the invention are characterized in the dependent subclaims.

The object is solved according to the invention in that a device for the photolithographic exposure of biological substances is created, comprising at least one light source, a bundle of light-guiding optical fibers and a control unit,

whereby each of the optical fibers can be controlled by light and/or light can be coupled to these fibers, independently of one another.

It is preferred that the light source emits monochromatic or continuous light in a wavelength range of 100 to 800 nm. It is particularly preferred that the light source is a laser, a luminous diode, a metal-vapor lamp, a gas-discharge lamp, a gas-excitation lamp, an incandescent-filament lamp or an arc lamp.

It is further advantageous that luminous diodes and/or optical switches are arranged for controlling the individual optical fibers.

It is particularly advantageous that the substances to be exposed are introduced directly at the ends of the optical fibers. However, it is also preferred that substances to be exposed are arranged on a separate support.

It is most especially preferred that substances to be exposed are arranged on a separate support, and that this support is a DNA chip, a PNA chip or a peptide chip.

According to the invention, the device preferably also has at least one detector.

It is thus preferred that at least one of the detectors is arranged in such a way that the latter detects the light used for exposure and/or at least one detector is arranged in such a way that it detects light reflected from the exposed substances and/or produced by fluorescence and that optical fibers and/or bundles of optical fibers are optionally provided for conducting light for the detectors. It is particularly preferred that the detectors are CCD detectors and/or CCD cameras.

It is very particularly preferred that a dynamic mask is provided for controlling the individual optical fibers. It is also particularly preferred that a set of static masks is provided for controlling the individual optical fibers.

A device according to the invention is most preferred, wherein the light source emits a spectrum of wavelengths that can effect the deprotection of nucleotides, nucleotide analogs and peptide nucleic acid building blocks for chain elongation and for constructing oligomers, and that a bundle of optical fibers is arranged between this light source and the substrate, in which light can be coupled selectively by targeted control, and that the solid phase on which the oligomer synthesis occurs is positioned precisely and rigidly behind the bundle of optical fibers, and that the solid phase on which the oligomer synthesis occurs is arranged in a chamber in which the solutions and/or reagents necessary for DNA or PNA synthesis can be introduced to this solid phase by additional devices.

It is preferred according to the invention that a separate support is arranged as the solid phase on which the oligomer synthesis occurs. It is further preferred according to the invention that the ends of the optical fibers themselves are the solid phase for conducting the oligomer synthesis.

Another subject of the present invention is a method for the photolithographic exposure of biological substances, wherein these substances are arranged on a surface or at the end of an optical fiber and exposed by means of light, which is guided by the optical fiber and originates from a light source, which is arranged at the other end of the optical fiber, whereby each point which lies opposite one end of the optical fiber is exposed independently of the other

points, whereby the exposure pattern is selected in advance by means of a control unit.

It is specifically preferred, for exposure of DNA or PNA chips, that light of wavelengths which cause the deprotection of nucleotides, nucleotide analogs and peptide nucleic acid building blocks for chain elongation and for construction of oligomers be used, and that a bundle of optical fibers is arranged between this light source and the substrate, in which [fibers], light is selectively coupled to each fiber by targeted control, and that the solid phase on which oligomer synthesis occurs is positioned precisely and rigidly behind the bundle of optical fibers, and that the solid phase on which the oligomer synthesis occurs is arranged in a chamber in which solutions and/or reagents that are necessary for DNA or PNA synthesis are introduced onto the solid phase by additional devices.

It is further preferred according to the invention that subsequent hybridizations are conducted with a target DNA after the oligomerization has been produced on the DNA or PNA chips.

Another subject of the invention is a method, wherein one uses a device according to the invention for conducting the method.

It has been found surprisingly that the device according to the invention makes possible a simple and moderately priced photolithographic production of DNA chips of high grid density with an exposure contrast of far greater than 1:100. In this way, the simple production of qualitatively superior DNA chips in any laboratory is made possible for the first time.

The device according to the invention and the method solve the object that was set forth in a completely novel manner by combination of commercially available components. It makes possible the inexpensive production of DNA chips in a quality that has not been previously possible.

The basic concept of the device and of the method according to the invention consists of the fact that a specific exposure pattern is produced on the substrate not by targeted masking of grid points by means of a static or dynamic mass, but rather light is introduced directly by means of an optical fiber light guide individually to each of the grid points to be exposed. Therefore, the end of an optical fiber must be introduced over each grid point such that when light is coupled to the fiber, the light exiting at the end precisely illuminates the corresponding grid point. Consequently, the number of optical fibers that are necessary corresponds precisely to the grid points that are provided. In order to be able to produce any desirable exposure pattern, an independent control of each individual optical fiber must be made of whether or not light is coupled to it at a given time point. By coupling or not coupling light in a targeted manner to the correct fibers, those grid points that must be activated can be exposed exclusively at each exposure step, while all others remain unexposed.

The targeted coupling of light into the correct fibers each time must be controlled in a fully automatic electronic manner, and thus the method can be conducted in a simple way. One possible technical solution is to introduce a light source that can be turned on and off at the beginning of each optical fiber, which belongs to just this one fiber (e.g., a laser diode of the correct wavelength).

Another possibility is the use of commercially available optical switches that can be controlled electrically. These involve a hardware component with 2 terminals or 2 optical fibers and an electrical control input. It can be determined by an electrical signal at the control input whether or not the two optical fibers will be optically combined. One optical switch and two optical fibers are thus necessary for each grid point. Light is permanently coupled to the free end of the first fiber, while the free end of the second fiber serves as the light output and is attached over the respective grid point. A single light source is sufficient for light coupling, if all input fibers are bundled correspondingly.

Both methods of targeted light coupling are equivalent for the electrical control. Only one control electronics unit is required, which can individually address each grid point. Basically, it does not matter whether light diodes or optical switches are controlled.

Another possibility for the targeted light coupling in the individual fibers of the optical fiber bundle is the use of automatically positioned static masks (e.g., photomasks or shadow masks) or an electronically controllable dynamic mask (e.g., an LCD), which is introduced between the light source and the input side of the fiber bundle. Any fiber inputs into which light will not be coupled at the respective exposure step can be masked in a targeted manner with the masks. The masks can be arranged geometrically in a different manner and particularly may be much larger than the array surface to be exposed, since the bundle of optical fibers can be fanned out or can be separated into individual fibers on the coupling side, as desired.

For the maximally attainable grid density of the chip, it does not matter how much space the light coupling system (individual light sources, optical switches, static or dynamic masks) requires. The grid density is only dependent on how densely the fiber ends on which the light emerges can be bundled. This possibility of geometrical packing represents the most essential advantage of the invention. In the case of a typical fiber diameter of approximately 100 micrometers, approximately 1000 grid points can be obtained per square centimeter on the exposure side, which is sufficient for many applications.

If it is too time-consuming to arrange the ends of the optical fibers that are to be introduced over the substrate in a uniform, rectangular lattice grid, one may also attach an unarranged fiber bundle over the substrate. The points on a chip produced in this way are then no longer grid-shaped, but are arranged randomly and irregularly. Nevertheless, for all chips, which have been produced by the same arrangement of optical fibers, the positions of the points are identical. Basically, one can know which type of oligomer has been synthesized at which position of the chip. It is sufficient for a given synthesis arrangement with a random bundling of light fibers to couple light sequentially to each individual optical fiber a single time and to establish the positions of the emitted light cone with a high-resolving CCD detector, which is placed in the plane of the substrate. A complete table with the assignment of all control addresses to the corresponding x-y substrate positions can be prepared in this way. This information is later used for evaluating all chips that are prepared with the corresponding arrangement.

For an evaluation according to the method of fluorescent labeling, one may optionally use the same unrastered arrangement of optical fibers, which has been used in the production, but in this case light is now not coupled to the other end of the fiber, but rather the fluorescent light occurring now in points on the substrate side is measured by means of photodetectors. For this purpose, a separate photodetector must be introduced at the position of the light source(s) at each fiber end. Such an optical reading system with optical fibers can considerably simplify chip detection in comparison with conventional detection methods by means of CCD detectors.

A very interesting and novel variant of application of the DNA chip synthesis method described here is the synthesis of oligomers directly onto the ends of the optical fibers instead of onto a separate substrate. This can be achieved by chemically preparing the end surfaces of the optical fibers through which the light is emitted in a way similar to the preparation of conventional DNA chip support surfaces. In this way, each end of the optical fiber is itself a small, independent support, on which one type of oligomer can be synthesized precisely with the usual photolithographic chemistry. The photoactivating light is thus no longer irradiated from outside onto the support surface, but is emitted directly at the support surface from the transparent, light-guiding support material. Instead of a single support surface with many different, small oligomer points, one now has a plurality of separate small support surfaces, each with one type of oligomer thereon. As in the case of conventional chips, the oligomer points must lie densely next to one another, and thus they can be used for an

efficient hybridization. This can be achieved, as described above, by dense bundling of the fiber ends.

With such a synthesis on the ends of optical fibers, the family of oligomer points that is produced remains inseparably connected to the device used for the production. Hybridization and subsequent detection are then also conducted at the ends of the optical fibers, whereby the optical fibers are again used for a fluorescent detection in the direction opposite to the readout of the fluorescent signals. After one synthesis-hybridization-detection cycle, the tips of the optical fibers can be chemically cleaned and the device can thus be made ready for a new synthesis.

The present invention will be explained in more detail on the basis of the attached drawing.

Here:

Fig. 1 shows the schematic arrangement of a first embodiment of the device of the invention, in which the fibers are controlled by optical switches;

Fig. 2 shows the schematic arrangement of a second embodiment of the device according to the invention, in which the control of the fibers is represented by individual light sources;

Fig. 3 shows the schematic arrangement during the exposure of a separate support (chip) and

Fig. 4 shows the schematic arrangement during exposure, whereby the substrate is found directly at the ends of the fibers.

A first example of embodiment of a device according to the invention is shown in Figure 1. The light from light source A is guided over the electrically controlled optical switch B onto the array support C by means of optical fiber F. The control S, preferably a computer, provides for the corresponding control of the individual switches B in a pregiven manner in the form of a dynamic or static mask.

A second example of embodiment of a device according to the invention is shown in Figure 2. The light is guided onto the array support C by means of the optical fiber F from a plurality of light sources A. The control S, preferably a computer, provides for the corresponding control of the individual switches A in a pregiven manner. Here also, the control can be produced in the form of a dynamic or static mask.

Figure 3 shows in detail how the individual substrate points E on the array support C are exposed by optical fibers F.

Figure 4 shows that the substrates are arranged directly at the ends of the optical fibers F.

It is clear to the person of average skill in the art how the individual components are to be arranged in a device according to the invention. Also, the corresponding programming of the control by means of computer programs is known in and of itself to the person of average skill in the art.

List of reference symbols

A: light source

B: electrically controlled optical switches

C: array support

D: substrate at the fiber ends

E: substrate points on the array support

F: optical fiber

S: control (computer)

Patent Claims

1. A device for the photolithographic exposure of biological substances, comprising at least one light source, a bundle of light-guide optical fibers, and a control unit, wherein each of the optical fibers can be controlled by light and/or light can be coupled to these fibers, independently of one another.

2. The device according to claim 1, further characterized in that the light source emits monochromatic or continuous light in a wavelength range of 100 to 800 nm.

3. The device according to claim 2, further characterized in that the light source is a laser, a luminous diode, a metal-vapor lamp, a gas-discharge lamp, a gas-excitation lamp, an incandescent-filament lamp or an arc lamp.

4. The device according to one of the preceding claims, further characterized in that luminous diodes and/or optical switches are arranged for the control of the individual optical fibers.

5. The device according to one of the preceding claims, further characterized in that the substances to be exposed are introduced directly at the ends of the optical fibers.

6. The device according to one of the preceding claims, further characterized in that the substances to be exposed are arranged on a separate support.

7. The device according to one of the preceding claims, further characterized in that the substances to be exposed are arranged on a separate support, whereby this support is a DNA chip, a PNA chip or a peptide chip.

8. The device according to one of the preceding claims, further characterized in that the device additionally comprises at least one detector.

9. The device according to claim 8, further characterized in that at least one of the detectors is arranged in such a way that it detects the light used for the exposure and/or at least one detector is arranged in such a way that it detects the light reflected from the exposed substances and/or produced by fluorescence and that optical fibers and/or bundles of optical fibers are optionally provided for light guiding for the detectors.

10. The device according to one of claims 8 or 9, further characterized in that the detectors are CCD detectors and/or CCD cameras.

11. The device according to one of the preceding claims, further characterized in that a dynamic mask is provided for the control of the individual optical fibers.

12. The device according to one of the preceding claims, further characterized in that a set of static masks is provided for the control of the individual optical fibers.

13. The device according to one of the preceding claims, further characterized in that the light source emits a spectrum of wavelengths that bring about

the deprotecting of nucleotides, nucleotide analogs and peptide nucleic acid building blocks for the elongation of the chain and for the construction of oligomers, and that between this light source and the substrate is arranged a bundle of optical fibers, to which light can be selectively coupled each time by targeted control, and that the solid phase on which the oligomer synthesis occurs is positioned precisely and rigidly behind the bundle of optical fibers, and that the solid phase on which oligomer synthesis occurs is arranged in a chamber in which the solutions and/or reagents necessary for the DNA or PNA synthesis can be introduced onto this solid phase by other devices.

14. The device according to claim 13, further characterized in that a separate support is arranged as the solid phase on which oligomer synthesis occurs.

15. The device according to claim 13, further characterized in that the ends of the optical fibers themselves are the solid phase for conducting the oligomer synthesis.

16. A method for the photolithographic exposure of biological substances, whereby the substances are arranged on a surface or at the end of an optical fiber and are exposed by means of light, which is guided by the optical fiber and which originates from a light source that is arranged at the other end of the optical fiber, whereby exposure is made at each point which lies opposite one end of the optical fiber, independently of the other

points, whereby the exposure pattern is selected in advance by means of a control unit.

17. The method according to claim 16, i.e., for the exposure of DNA or PNA chips, further characterized in that light of wavelengths which cause the deprotecting of nucleotides, nucleotide analogs and peptide nucleic acid building blocks for the elongation of the chain and for the construction of oligomers is used and that between this light source and the substrate, a bundle of optical fibers is arranged, to which light is selectively coupled each time by targeted control and that the solid phase on which the oligomer synthesis occurs is positioned precisely and rigidly behind the bundle of optical fibers and that the solid phase on which the oligomer synthesis occurs is arranged in a chamber in which the solutions and/or reagents necessary for the DNA or PNA synthesis are introduced onto this solid phase by other devices.

18. The method according to claim 16, further characterized in that subsequent hybridizations are conducted with a target DNA after the oligomerization has been produced on the DNA or PNA chips.

19. The method according to claim 16, further characterized in that a device according to claim 1 is used for conducting the method.

Abstract

A device and a method for the photolithographic exposure of biological substances is described, which comprises at least one light source, a bundle of optical fibers and a control unit, whereby each of the optical fibers can be controlled by light independently from one another and/or light can be coupled to each fiber independently.

The device is particularly suitable for the exposure of DNA, PNA or peptide chips.

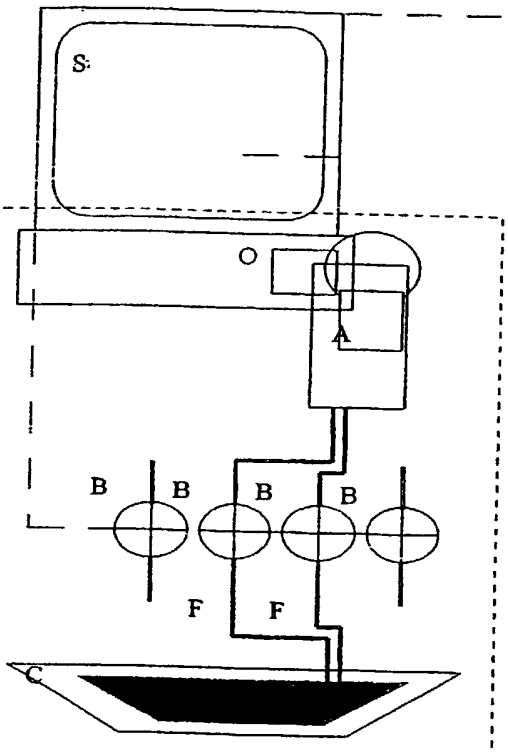

Fig.1

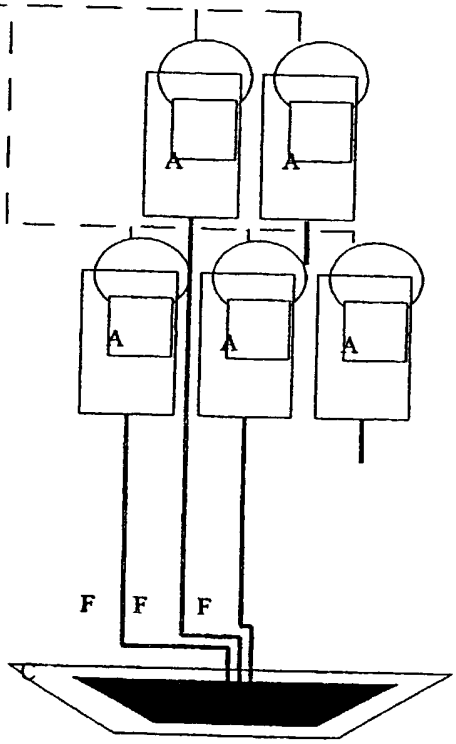

Fig.2

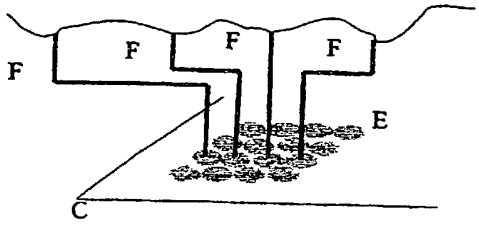

Fig.3

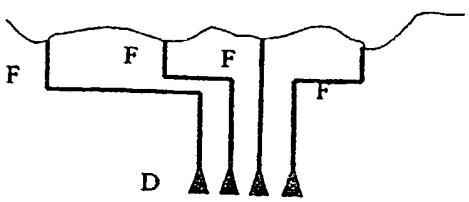

Fig.4

Attorney Docket No. 81785

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled, DEVICE AND METHOD FOR PHOTOLITHOGRAPHICALLY IRRADIATING BIOLOGICAL SUBSTANCES the specification of which: (check one)

[ ] is attached hereto.
[ ] was filed on and assigned Serial No:
[X] was filed as PCT International Application No. PCT/DE00/01540 on May 12, 2000, and has been assigned U.S. Patent Application Serial No. 09/980,194.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed
199 22 941.4	GERMANY	14 May 1999	[X] yes [ ] no
(number)	(country)	(day/month/year filed)	
			[ ] yes [ ] no
(number)	(country)	(day/month/year filed)	

I hereby claim the benefit under Title 35, United States Code, 119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION NUMBER	FILING DATE:

81785

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or under Title 35, United States Code, § 365(c) of any PCT International application designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclosed material information as defined in Title 37, Code of Federal Regulations 1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(application number)	(filing date)	(Status - patented, pending, abandoned)
(application number)	(filing date)	(Status - patented, pending, abandoned)
(application number)	(filing date)	(Status - patented, pending, abandoned)

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that any statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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